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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,224	05/17/2005	Mahendra S. Rao	UT-0048	1620

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/502,224	RAO ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of July 2, 2008, to the non-final action dated November 11, 2008, has been entered. Claims 1-10 are pending in the Application. Claims 5-10 remain withdrawn from consideration, with traverse. Claim 1 has been amended. No claims were cancelled or newly added. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 1-4 are currently under examination.

Response & Withdrawn Claim Objection

Claim 1 was objected to for containing several language informalities, in the previous office action dated May 16, 2008. Applicants have amended the claim to remove the objectionable language, thereby obviating the ground for objection. Thus, the objection is hereby withdrawn.

Response & Withdrawn Claim Rejections - 35 USC § 112- New Matter

Claim 1 was rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement and introducing new matter, in the previous office action dated May 16, 2008. Applicants have amended the claim to delete the new matter, thereby obviating the ground for rejection. Thus, the rejection is hereby withdrawn.

New Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's claim amendments have necessitated the following new ground of rejection.

Claims 2-4 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 3 recite the limitation "the pure homogenous population of astrocytes restricted precursor cells of claim 1" in the first and second lines of the claims. There is insufficient antecedent basis for this limitation in the claims. Claim 4 depends from claim 3, and has therefore been included in the rejection.

Response & Maintained Claim Rejections - 35 USC § 112 – Scope of Enablement

Claims 1-4 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The rejection set forth on pp. 4-9 of the previous office action dated May 16, 2008 is maintained, for reasons of record, because the specification while being enabling for a culture of mammalian neural progenitor cells from embryonic or fetal tissue, or a culture of mammalian ES cells that may be differentiated into astrocytes, oligodendrocytes and neurons under appropriate differentiation conditions, does not reasonably provide an enablement for an isolated population of mammalian astrocyte restricted precursor cells, being CD44 and nestin immunoreactive, A2B5 or E-NCAM negative, and generating astrocytes but not oligodendrocytes or glial cells, or a method of isolating the same from embryonic or fetal tissue, ES cell cultures, or glial restricted precursor cells, as claimed.

The previous office actions set forth issues with regards to the deficiencies in the instant specification in providing an enabling disclosure for the instantly claimed cells and methods, and indicating an absence of an enabling disclosure for a pure homogeneous population of mammalian astrocyte restricted precursor cells, being CD44 immunoreactive and generating astrocytes but not oligodendrocytes, or a method of isolating the same from embryonic or fetal tissue, ES cell cultures, or glial restricted precursor cells, because the specification states: "The astrocyte restricted precursor cells of the present invention do not express A2B5. Further these cells differ from stem and progenitor cell populations in their expression of CD44 and their ability to differentiate into astrocytes…but not oligodendrocytes" (lines 14-25, p. 4), that is not accord with the observations in the working examples. The examples show that at least for the

human neuroepithelial progenitor cells, it is clear that following marker sorting, the same cell population may be differentiated to give rise to astrocytes, oligodendrocyte and neurons, depending on alterations in culture conditions. Hence, the human neuroepithelial progenitor cells are not astrocyte restricted, as they may differentiate into additional cells types. Additionally, page 8 of the instant specification acknowledges that CD44 expression was limited to astrocytes (line 14). Moreover, the progenitor cells are capable of differentiation into oligodendrocytes, as taught by the specification, contrary to the language of the instant claims.

Applicants disagree with the rejection, and citing various sections of the specification as providing support for the instantly amended claim 1, argue that the disclosure, including Examples 4, 6, 7 and 8 of the Application discloses how to make and use the instant invention as required to meet the enablement requirements of 35 U.S.C. 112, first paragraph. Applicants' arguments have been fully considered, but are not found persuasive.

As an initial matter it is noted that the instant claims are directed to an isolated population of mammalian cells that are astrocyte restricted. The term astrocytes restricted means that the cells have been terminally committed to differentiate into astrocytes and no other cell types. Such is not consistent with the teachings of the specification, including the Examples. The inconsistency is further highlighted in instant claim 2, directed to a method for isolating astrocyte-restricted precursor cells from glial-restricted precursor cells. Glial-restricted precursor cells should by definition be committed to differentiating into both astrocytes and oligodendrocytes, and yet are claimed as containing astrocyte-restricted precursor cells. Further, the glial restricted precursor cells may arise from differentiation of neuroepithelial progenitor cells.

With regards to the cited Examples, Examples 6 relates to human ES cell culture maintenance and provides no information regarding the issues raised in the rejection; Example 7 related to the formation of embryoid bodies from human ES cells and Example 8 describes general immunocytochemistry procedures. Thus, the only pertinent Example is Example 4, wherein mixed cell cultures of human fetal cells were commercially obtained and were shown to be A2B5 and E-NCAM negative prior to differentiation, followed by a description of conditions

for oligodendrocyte differentiation. Example 2 fails to disclose the isolation of a population of astrocyte restricted precursor cells.

With respect to the reference of Lodie et al., Applicants argue that its teachings are irrelevant to the instant claimed invention. Such is not found persuasive, because Lodie et al. disclose that in human bone marrow derived stem cells, CD44 expression is variable, and apparently dependent on serum concentration (Abstract). The authors further demonstrated that CD44 expression did not have an impact on the ability of the cells to ultimately differentiate toward the neural lineage and appeared to be dependent on serum concentration as demonstrated by other researchers (pp. 749-750, bridging). Lodie et al. additionally state that stromal and mesenchymal stem cells have additionally been isolated from bone marrow and have the capacity to differentiate along all different cell lineages, including the neural lineage. The instant claims encompass CD44 immunoreactive cells that can generate neural cells under appropriate differentiation conditions. The art of Lodie et al. was provided to show the unpredictability of the instantly claimed invention. Therefore, the variable CD44 immunoreactivity is highly relevant to the instant invention, contrary to Applicants' assertion.

The previous office action indicated that Applicants had stated on the record, that the wording Examples were not provided as enablement for the instant claimed cells, when the specification states: "The following nonlimiting examples are provided to further illustrate the present invention." (p. 15, lines 14-15). The office action further indicated that Applicants have essentially argued that a person of skill in the art should not regard the working Examples as enabling for the instantly claimed invention, and thus particularly ignore Example 2, titled: "Isolation of Human Neuroepithelial Precursor Cells", that includes the isolation of A2B5 negative cells. However, a person of skill in the art having considered the teachings of the entire specification, would not find sufficient guidance for making the instantly claimed pure homogenous population of precursor cells that are at once A2B5 negative and CD44 positive, and restricted to only the astrocyte lineage, thus lacking the ability to generate oligodendrocytes. A person of ordinary skill having considered the teachings of the instant specification and the prior art would merely conclude that neuroepithelial precursor cells can differentiate into astrocytes, oligodendrocytes or other neural cells depending on culture conditions, and that any

intermediate cell population of the final product (astrocytes) was not purified as a pure homogenous population of astrocyte restricted cells at the time of the instant invention by Applicants. As the initial neuroprogenitor cells and their differentiation to the end product (astrocytes) were known and described in the prior art, any potential intermediates in the differentiation process must necessarily also be present. However, as indicated in MPEP 2112, The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364,1368 (Fed. Cir. 2004).

Applicants argue that those skilled in the art recognize that the astrocyte restricted precursor cells are different from cells referred to as human neuroepithelial precursor cells. In response, it is noted that such is not at issue. The issue is whether the specification enables the skilled artisan to isolate the astrocyte restricted mammalian precursor cells, having the cell marker characteristics instantly claimed, and such has not been demonstrated or enabled in the absence of further undue experimentation.

Therefore, the rejection of claims 1-4 is maintained in modified form, for reasons of record and the preceding discussion.

Response & Maintained Claim Rejections - 35 USC § 102

Claims 1-4 stand rejected under 35 U.S.C. 102(e) as being anticipated by Carpenter (U.S. Patent No.: 6,833,269; filed May 31, 2001). The rejection set forth on pp. 8-10 of the office action dated March 12, 2007, pp. 5-6 of the office action dated November 1, 2007, and pp. 9-12 of the previous office action dated May 16, 2008 is maintained for reasons of record.

The instant claims embrace an isolated population of mammalian astrocyte restricted precursor cells, isolated from mammalian embryonic or fetal tissue or mammalian embryonic stem (ES) cells cultures, being immunoreactive for CD44 and nestin, but not expressing A2B5 or E-NCAM. The claim language of "astrocyte restricted" is interpreted to be non-limiting because the ability of the cells to differentiate into astrocytes, but not oligodendrocytes is a consequence of culturing conditions, as taught by the instant specification (Example 3, p. 17). Moreover, a

precursor cell treated under differentiating conditions would necessarily become committed to a particular differentiation path of cell specific lineage, immediately prior to terminal differentiation.

The prior art of Carpenter has been applied commensurate with the enabled scope of the claims indicated above and to the extent that the claims embrace a population of mammalian precursor cells isolated from mammalian embryonic stem (ES) cells cultures, that may be differentiated to generate astrocytes.

Carpenter teaches methods for producing neural progenitor cells by culturing, expanding and differentiating embryonic stem cells into a variety of different neural phenotypes in a cocktail of growth conditions (Abstract). Specifically, human embryonic stem cells (hES) are maintained in a feeder-free system on plates coated with Matrigel® in medium composed of 80% KO DMEM (knockout) and 20% serum replacement medium supplemented with 1% non-essential amino acids, 1mM glutamine, 0.1 mM β-mercaptoethanol and 4ng/ml bFGF, (the media conditioned by culturing embryonic fibroblasts) (column 21). The cells are expanded by serial passaging, removed and used formation of embryoid bodies (column 21). Following immunosorting and magnetic separation, the "cells are maintained on plates coated with poly-lysine and laminin in DMEM/F12 (Biowhittaker) supplemented with N2 (Gibco 17502-014), B27 (Gibco 17504-010) and the factors indicated. Source of the factors is shown in Table 2." (column 22). In Example 5, Carpenter et al. teach: "To generate terminally differentiated neurons, the first stage of differentiation was induced by forming embryoid bodies in FBS medium with or without 10 μM retinoic acid (RA). After 4 days in suspension, embryoid bodies were plated onto fibronectin-coated plates in defined medium supplemented with 10 ng/mL human EGF, 10 ng/mL human bFGF, 1 ng/mL human PDGF-AA, and 1 ng/mL human IGF-1. After 3 days, many cells with neuronal morphology were observed. The neural precursors were identified as cells positive for BrdU incorporation, nestin staining, and the absence of lineage specific differentiation markers. Putative neuronal and glial progenitor cells were identified as positive for polysialylated NCAM and A2B5…The cell populations were further differentiated by replating the cells in a medium containing none of the mitogens, but containing 10 ng/mL Neurotrophin-3 (NT-3) and 10 ng/mL brain-derived neurotrophic factor (BDNF). Neurons with

extensive processes were seen after about 7 days." (column 28). The method of Carpenter provides for the differentiation of pluripotent ES cells into cells of the neuronal or glial lineage. Precursor cells for either lineage, provide a source for generating additional precursor cells, neurons, astrocytes or oligodendrocytes (column 3; first paragraph), as well as neurons that include glial cells, astrocytes, dopaminergic cells and motor neurons (Abstract, column 19 and claim 18).

While markers such as A2B5 are discussed by Capenter et al., CD44 immunoreactivity was not assessed by the authors. However, as stated above, CD44 expression is variable, and apparently dependent on serum concentration and culture conditions. Further the expression of CD44 is an inherent feature of the mammalian ES cell derived precursor cells of Carpenter et al. and the expression of nestin is further a property of a precursor cell having differentiated into astrocyte, and must necessarily be present under the culture conditions of the instant invention. As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Applicants traverse the rejection, arguing the claims have been amended to recite that the astrocyte-restricted precursor cells which express CD44 and nestin and do not express A2B5 or E-NCAM. In contrast, cells of Carpenter express A2B5, NCAM or both. Applicants' arguments have been fully considered, but are not found persuasive.

As indicated, the rejection of the claims over the prior art of Carpenter et al. is applicable to the enabled scope of the invention, and that the instant specification has expressly disclosed as differentiating oligodendrocytes, not astrocytes. Further, as previously indicated, the limitation for astrocyte-restricted neuroprogenitor cells is not afforded patentable weight in view of the foregoing discussion.

It is noted again that the generation of oligodendrocytes, astrocytes and neurons are dependent on culture conditions, in a similar manner disclosed in the Applicants' specification.

Carpenter teaches methods for producing neural progenitor cells by culturing, expanding and differentiating embryonic stem cells into a variety of different neural phenotypes in a cocktail of growth conditions (Abstract). The method of Carpenter provides for the differentiation of pluripotent ES cells into cells of the neuronal or glial lineage. Precursor cells for either lineage, provide a source for generating additional precursor cells, neurons, astrocytes or oligodendrocytes (column 3; first paragraph), as well as neurons that include glial cells, astrocytes, dopaminergic cells and motor neurons (Abstract, column 19 and claim 18). Additionally, CD44 expression is variable, and apparently dependent on serum concentration and culture conditions. Further the expression of CD44 is an inherent feature of the mammalian ES cell derived precursor cells of Carpenter et al. and must necessarily be present depending on the culture conditions. Nestin is a neural specific marker and is expressed as a result of the differentiation of the ES cells along the neural pathway.

Both the starting material (ES cell) and the final product (astrocytes) were described by Carpenter et al. along with the method of differentiating said ES cells. Thus, even if Applicants had demonstrated possession of an astrocyte restricted precursor cell, such would necessarily be present in the culture of Carpenter et al. as an intermediate.

Therefore, the rejection of claims 1-4 is maintained for reasons of record and the preceding discussion.

Conclusion

Claims 1-4 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633